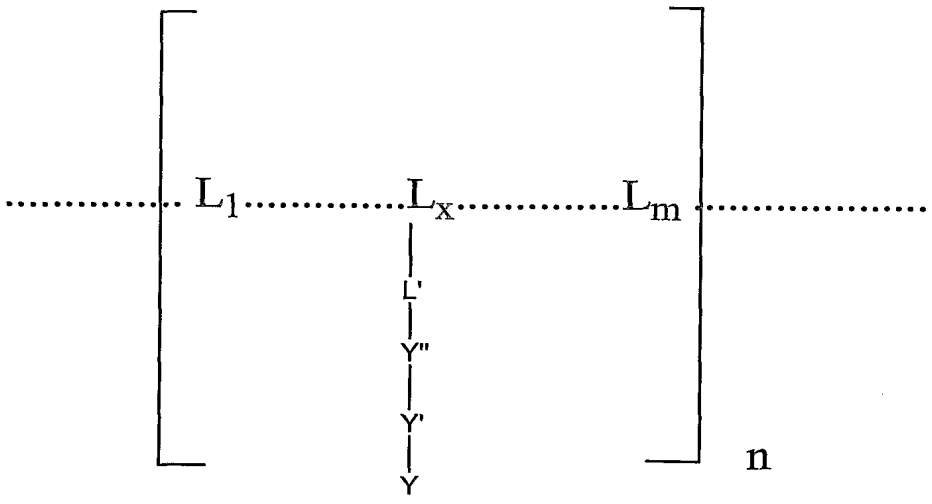
Claims:

1. A method of preparing covalent or catalytic antibodies, comprising: producing in an organism antibodies to a covalently reactive polypeptide antigen analogue (pCRA) of formula (1):



(1)

wherein, $L_1 \ldots Lx \ldots Lm$ are components defining an antigenic determinant,

Lx is a component unit of the antigenic determinant selected from the group consisting of an amino acid residue, sugar residue, a fatty acid residue and a nucleotide,

L' is a functional group of Lx,

Y'' is atom, covalent bond or linker,

Y' an optional charged or neutral group

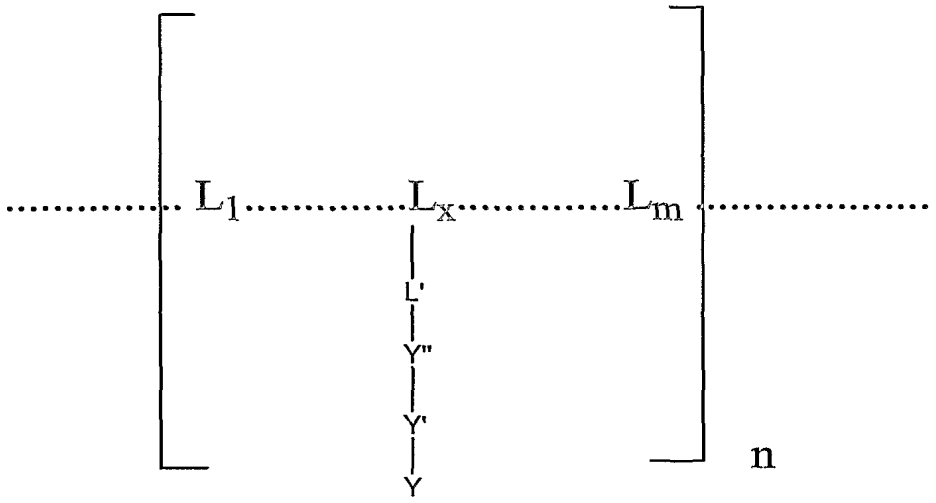
Y is a covalently reactive electrophilic group that reacts specifically with an antibody that binds to said antigenic determinant,

optionally, Y", Y' or Y contains a water-binding group as a terminal or internal component;

n is an integer from 1 to 1000; and

m is from 4 to 30.

2. A water-binding, covalently reactive polypeptide antigen analogue (pCRAW) of formula (1):



wherein, $L_1 \ldots Lx \ldots Lm$ are components defining an antigenic determinant,

Lx is a component unit of the antigenic determinant selected from the group consisting of an amino acid residue, sugar residue, a fatty acid residue and a nucleotide,

L' is a functional group of Lx,

Y'' is atom, covalent bond or linker,

Y' an optional is a charged or neutral group

Y is a covalently reactive electrophilic group that reacts specifically with an antibody that binds to said antigenic determinant,

Y", Y' or Y contains a water-binding group as a terminal or internal component;

n is an integer from 1 to 1000; and

m is from 4 to 30.

3. The pCRAW of claim 2, wherein the water-binding group is composed of a site that binds a metal ion which chelates one or more water molecules.

4. The pCRAW of claim 3, in which the metal is zinc, copper, nickel, cobalt, calcium or magnesium.

5. The pCRAW of claim 2, in which the metal binding group is selected from: -$(His)_n$- where n=2 or more, -Cys-X-Cys-Cys- or -Cys-X-Cys- wherein X is an amino acid residue, ethylene diamine tetraacetic acid or diaminomethyl pyridine.

6. The method of claim 1, wherein binding of the antibodies to a polypeptide antigen is resistant to dissociation by a denaturant that disrupts non-covalent antigen binding.

7. The method of claim 1, wherein the binding of the antibodies to a polypeptide antigen is resistant to dissociation by 2% sodium dodecyl sulfate.

8. The method of claim 1, wherein the polypeptide antigen is HIV-1 gp120.

9. The method of claim 1, wherein the antibodies catalyze the cleavage of a peptide bond in a polypeptide antigen.

10. The method of claim 9, wherein the polypeptide antigen is HIV-1 gp120.

11. The method of claim 1, wherein the antibodies are polyclonal antibodies identified in the serum of said organism by:

a) screening and selection for covalently binding antibodies; and

b) screening and selection for catalytic activity.

12. The method of claim 1, wherein the antibodies are monoclonal antibodies or antibody fragments obtained from lymphocytes of said organism by steps comprising:

a) preparing a library of hybridoma cell lines, virus-transformed cell lines or immunoglobulin fragment genes expressed from a vector;

b) screening for covalent activity of antibodies or antibody fragments by their binding to an antigenic pCRA or a polypeptide;

c) screening for catalytic hydrolysis of a polypeptide by the antibodies or antibody fragments of step a) and step b); and

d) purifying the antibodies or the antibody fragments.

13. The method of claim 12, in which the antigenic pCRA is the CRA derivative of gp120, VIP, Factor VIII, epidermal growth factor receptor, CD4, β-amyloid peptide 1-40 or β-amyloid peptide 1-42.

14. The method of claim 12, in which the polypeptide is gp120, VIP, Factor VIII, epidermal growth factor receptor, CD4, β-amyloid peptide 1-40 or β-amyloid peptide 1-42.

15. The method of claim 12, wherein the organism is a transgenic mouse expressing human antibody genes.

16. The method of claim 12, wherein the organism is a mouse.

17. The method of claim 12, wherein the vector is selected from the group consisting of phage display vectors, retroviral display vectors, yeast display vectors, bacterial display vectors and mammalian display vectors.

18. The method of claim 12, wherein the antibody fragments are single chain Fv fragments expressing covalent or catalytic activity isolated by steps comprising:

a) preparation of the immunoglobulin VL and VH cDNA by reverse-transcriptase polymerase chain reaction;

b) cloning the VL and VH cDNA in a vector in a form enabling their expression as single chain Fv fragments expressed on the surface of a display vector;

c) contacting the vector particles with immobilized pCRA of claim 1, removal of unbound vector particles by washing, and expression of the Fv genes from the pCRA-bound vector particles in soluble form in prokaryotic or eukaryotic cells;

d) screening the soluble Fv constructs for covalent antigen binding activity;

e) screening the soluble Fv constructs for catalytic activity.

19. The method of claim 12, wherein lymphocytes are obtained by steps comprising:

a) contacting the lymphocytes with a pCRA;

b) separating lymphocytes that are bound to the pCRA from lymphocytes that are not bound to the pCRA.

20. The method of claim 19, wherein the pCRA contains a fluorescent group or is detected using a fluorescent probe and pCRA-bound lymphocytes are separated by flow cytometry.

21. The method of claim 1, wherein the antibodies belong to the IgG, IgM, IgD, IgA or IgE classes.

22. The method of claim 1, wherein the antibodies are fragments of IgG, IgM, IgD, IgA or IgE.

23. The method of claim 1, wherein [L_1...Lx...Lm] represents an antigenic determinant of a microbial protein.

24. The method of claim 1, wherein [L_1...Lx...Lm] represents an antigenic determinant of the HIV-1 protein.gp120.

25. The method of claim 1, wherein [L_1...Lx...Lm] represents an antigenic determinant of a human, animal or plant protein.

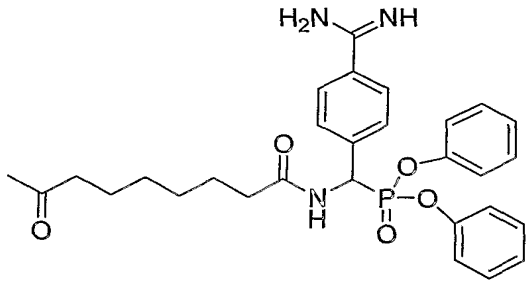
26. The method of claim 1, wherein [L_1...Lx...Lm] represents an antigenic determinant of vasoactive intestinal peptide.

27. The method of claim 1, wherein [L_1...Lx...Lm] represents an antigenic determinant of an antigen that is over-expressed on cancer cells.

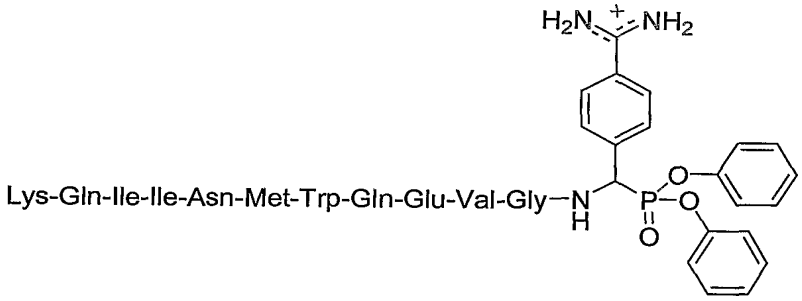
28. The method of claim 1, wherein [L_1...Lx...Lm] represents an antigenic determinant of the epidermal growth factor receptor.

29. The method of claim 1, wherein n is from 1 to 23.

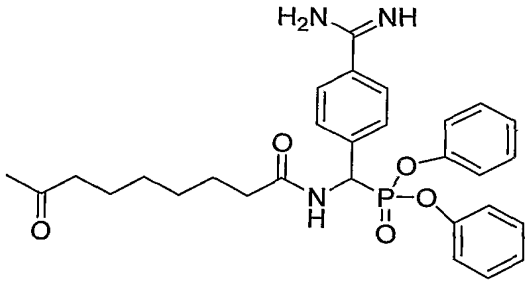
30. The method of claim 1, wherein the pCRA is gp120 derivatized at the Lys side chain amino groups at a density of 23 moles/mole protein with:



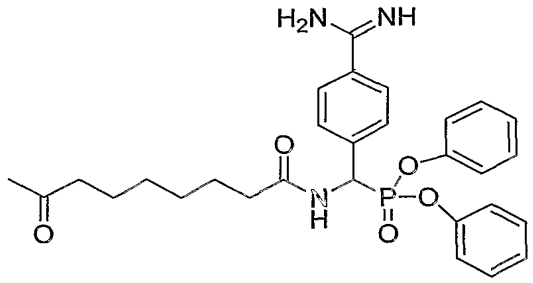
31. The method of claim 1, wherein the pCRA is the following gp120 peptidyl derivative:



32. The method of claim 1, wherein the pCRA is vasoactive intestinal peptide derivatized at the Lys20 side chain with:



33. The method of claim 1, wherein the immunogenic determinant is derived from the soluble extra-cellular domain of epidermal growth factor receptor, soluble extra-cellular domain of CD4, Factor VIII, β-amyloid peptide 1-40 or β-amyloid peptide 1-42, each derivatized at Lys side chains with:



34. Monoclonal IgG antibody clones YZ-18, YZ-20 and YZ-24 that catalyze the cleavage of gp120.

35. Monoclonal IgG antibody clones YZ-18, YZ-19, YZ-20, YZ-21, YZ-22, YZ-23 and YZ-24 that bind the gp120-CRA of claim 30 and the binding is resistant to dissociation with 2% SDS.

36. Monoclonal IgG antibody clones YZ-18, YZ-19, YZ-20, YZ-21, YZ-22, YZ-23 and YZ-24 that bind gp120 and the binding is resistant to dissociation with 2% SDS.

37. Full-length IgG, IgM and IgA antibodies prepared from the antibody fragments of claim 12, prepared by steps comprising:

a) insertion of the VL and VH domain cDNA at the 5' side of Ig constant domains contained in an expression vector by nucleic acid digestion and ligation procedures;

b) growth of the vector in a prokaryotic or eukaryotic host cell, extraction of the full-length antibodies from the culture medium or the cellular contents and purification of said antibodies.

38. A method of obtaining monoclonal covalent antibodies, catalytic antibodies, covalent antibody fragments or catalytic antibody fragments from the lymphocytes of organisms with autoimmune disease, organisms with alloimmune disease, organisms without known disease or transgenic mice expressing human antibody genes comprising the steps:

a) preparing a library of hybridoma cell lines, virus-transformed cell lines or immunoglobulin fragment genes cloned in and expressed from a vector;

b) screening and selection for covalent activity of antibodies or antibody fragments by binding to an antigenic pCRA of claim 1 or a polypeptide;

c) screening and selection for catalytic hydrolysis of a polypeptide by the antibodies or antibody fragments; and

d) purifying the antibodies or the antibody fragments.

39. The method of claim 38, wherein the antibodies hydrolyze peptide bonds.

40. The method of claim 38, wherein the antibodies hydrolyze peptide bonds in superantigenic polypeptides.

41. The method of claim 38, wherein the antibodies hydrolyze gp120.

42. The method of claim 38, wherein the antibodies hydrolyze CD4.

43. The method of claim 38, wherein the antibodies hydrolyze β-amyloid peptides.

44. The method of claim 38, wherein the antibodies hydrolyze β-amyloid peptides 1-40 and 1-42.

45. The method of claim 38, wherein the autoimmune disease is systemic lupus erythematosus.

46. The method of claim 38, wherein the immunoglobulin fragments are the VL and VH domains linked by a peptide linker.

47. The method of claim 38, wherein the immunoglobulin fragments are the light chain subunits.

48. The method of claim 38, wherein the vector is selected from the group consisting of phage display vectors, retroviral display vectors, yeast display vectors, bacterial display vectors and mammalian display vectors.

49. The method of claim 38, wherein the display vector is M13 phagemid vector pHEN2 or pCANTAB5his6.

50. The method of claim 38, wherein the antibody fragments are single chain Fv fragments or light chains expressing covalent or catalytic activity isolated by steps comprising:

a) preparing the immunoglobulin VL cDNA, VH cDNA and light chain cDNA by reverse-transcriptase polymerase chain reaction using as template the RNA from lymphocytes;

b) cloning the VL and VH cDNA in a form enabling their expression as single chain Fv fragments expressed on the surface of a display vector;

c) cloning the light chain cDNA in a vector in a form enabling their expression as light chains expressed on the surface of a display vector;

d) contacting the vector particles with immobilized pCRA of claim 1, removal of unbound vector particles by washing, and expressing the Fv cDNA or light chain cDNA from the pCRA-bound vector particles in soluble form in prokaryotic or eukaryotic cells;

e) screening the soluble Fv or light chain constructs for covalent antigen binding activity;

f) screening the soluble Fv or light chain constructs for catalytic activity.

51. Full-length IgG, IgM and IgA antibodies prepared from the Fv fragments of claim 38 prepared by steps comprising:

a) insertion of the VL and VH domain cDNA at the 5' side of Ig constant domains contained in an expression vector by nucleic acid digestion and ligation procedures;

b) growth of the vectors in a prokaryotic or eukaryotic host cell, extraction of the full-length antibodies from the culture medium or the cellular contents and purification of said antibodies.

52. Full-length IgG, IgM and IgA antibodies prepared from the light chain fragments of claim 38 prepared by steps comprising:

a) insertion of the light chain cDNA into an expression vector by nucleic acid digestion and ligation procedures;

b) insertion of the VH domain of gp120 binding antibodies at the 5' side of an IgG heavy chain constant domain contained in an expression vector by nucleic acid digestion and ligation procedures;

c) growth of the vectors in a prokaryotic or eukaryotic host cell, extraction of the

full-length antibodies from the culture medium or the cellular contents and purification of said antibodies.

53. The method of claim 38, wherein lymphocytes are obtained by steps comprising:

a) contacting the lymphocytes with a pCRA;

b) separating lymphocytes that are bound to the pCRA from lymphocytes that are not bound to the pCRA.

54. The method of claim 53, wherein the pCRA contains a fluorescent group or is detected using a fluorescent probe and pCRA-bound lymphocytes are separated by flow cytometry.

55. The method of claim 38, wherein the antibodies belong to the IgG, IgM, IgD, IgA or IgE classes.

56. The method of claim 38, wherein [L_1...Lx...Lm] in the pCRA represents an antigenic determinant of a microbial protein.

57. The method of claim 38, wherein [L_1...Lx...Lm] in the pCRA represents an antigenic determinant of the HIV-1 protein.gp120.

58. The method of claim 38, wherein [L_1...Lx...Lm] in the pCRA represents an antigenic determinant of a human, animal or plant protein.

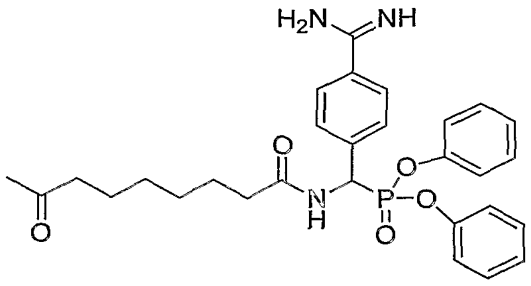
59. The method of claim 38, wherein [L_1...Lx...Lm] in the pCRA represents an antigenic determinant of vasoactive intestinal peptide.

60. The method of claim 38, wherein [L_1...Lx...Lm] in the pCRA represents an antigenic determinant of an antigen that is overexpressed on cancer cells.

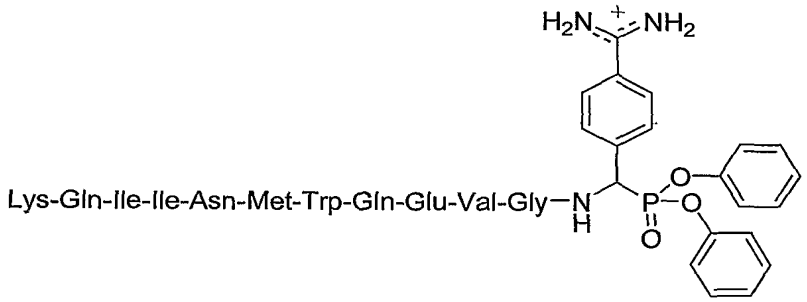
61. The method of claim 38, wherein [L_1...Lx...Lm] in the pCRA represents an antigenicc determinant of the epidermal growth factor receptor.

62. The method of claim 38, wherein n is from 1 to 23.

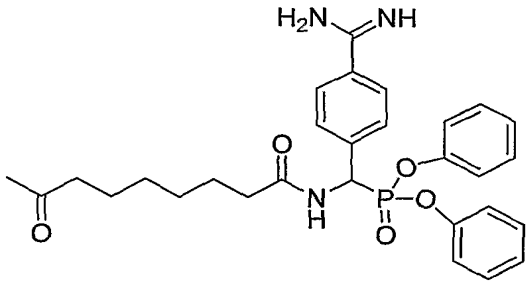
63. The method of claim 38, wherein the pCRA is gp120 derivatized at the Lys side chain amino groups at a density of 23 moles/mole protein with:



64. The method of claim 38, wherein the pCRA is the following gp120 peptidyl derivative:

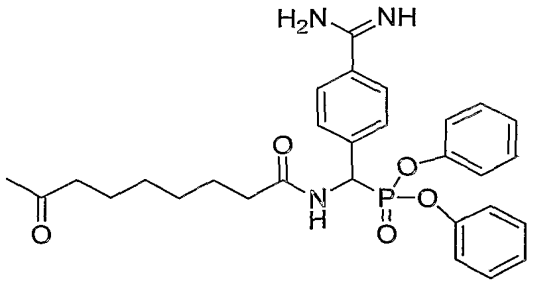


65. The method of claim 38, wherein the pCRA is vasoactive intestinal peptide derivatized at the Lys20 side chain with:



66. The method of claim 38, wherein the immunogenic determinant is derived from the soluble extra-cellular domain of the epidermal growth factor receptor, soluble extra-cellular domain of CD4, Factor VIII, β-amyloid peptide 1-40 or β-amyloid peptide 1-42,

each derivatized at Lys side chains with:



67. A method to improve the covalent or catalytic activity of the antibody fragments of claim 12, comprising the steps:

a) introducing mutations in the VL and VH domains;

b) display of the resultant antibody fragments on the surface of a display vector;

c) contacting the vector particles with the pCRAW, and removal of unbound vector particles

d) expressing the antibody fragments in soluble form in prokaryotic or eukaryotic cells;

d) screening the antibody fragments for covalent antigen binding activity;

e) screening the antibody fragments for catalytic activity.

68. The method to improve the covalent or catalytic activity of the antibody fragments of claim 38, comprising the steps:

a) introducing mutations in the VL and VH domains;

b) display of the resultant antibody fragments on the surface of a display vector;

c) contacting the vector particles with the pCRAW, and removal of unbound vector particles

d) expressing the antibody fragments in soluble form in prokaryotic or eukaryotic cells;

d) screening the antibody fragments for covalent antigen binding activity;

e) screening the antibody fragments for catalytic activity.

69. A method for passive immunotherapy of a disease, comprising:

a) administering a therapeutically effective amount of antibodies having covalent or catalytic activity specific for an antigen associated with a medical disorder in the patient, said antibody having been produced by the method of claim 1; and

b) repeating step a) as necessary for maintenance therapy.

70. A method for passive immunotherapy of a disease, comprising:

a) administering a therapeutically effective amount of antibodies having covalent or catalytic activity specific for an antigen associated with a medical disorder in the patient, said antibody having been produced by the method of claim 38; and

b) repeating step a) as necessary for maintenance therapy.

71. The method of claim 1, wherein the antibody is directed to gp120 for immunotherapy of HIV-1 infection.

72. The method of claim 1, wherein the antibody is directed to an hepatitis C virus protein gp120 for immunotherapy of hepatitis infection.

73. The method of claim 1, wherein the antibody is directed to a β-amyloid peptide for immunotherapy of Alzheimer's disease.

74. The method of claim 1, wherein the antibody is directed to the epidermal growth

factor receptor for immunotherapy of cancer.

75. The method of claim 1, wherein the antibody is directed to Factor VIII for immunotherapy of blood coagulation disorders.

76. A method for stimulating production of prophylactic antibodies in an organism, having covalent or catalytic activity specific for an antigen associated with a medical condition in the organism, comprising the steps of:

a) administering to an organism a vaccine containing an immunogenic amount of a pCRA prepared from said antigen as of claim 1;

b) repeating step a) as necessary to ensure effective antibody production.

77. The method of claim 76, in which the medical disorder is a microbial disease and the pCRA is prepared from a constituent protein of the microbe.

78. The method of claim 77, in which the medical disorder is HIV-1 infection and the pCRA is prepared from gp120.

79. A method of treating a medical disorder in a patient by inhibiting the action of a catalytic antibody, comprising the steps of:

a) administering to said patient a therapeutic amount of a pCRA in which the antigenic determinant is derived from an epitope irreversibly bound by said catalytic antibody;

b) assessing said patient for inactivation of said catalytic antibody; and

c) repeating step a) as necessary to maintain inhibition of said action of said catalytic antibody.

80. The method of claim 79, wherein said disease state is an autoimmune disease.

81. The method of claim 80, wherein said autoimmune disease is selected from the group consisting of autoimmune thyroiditis, systemic lupus erythmatosus, systemic sclerosis, asthma, rheumatoid arthritis, mixed connective disease, Reiter's syndrome, Sjogren's syndrome, vasculitis, and bird shot retinopathy.

82. The method of claim 79, wherein said medical disorder is a lymphoproliferative disorder.

83. The method of claim 82, wherein said lymphoproliferative disorder is selected from the group consisting of multiple myeloma, acute lymphoblastic leukemia, lymphoblastic lymphoma, small lymphocytic lymphoma, lymphoplasmacytoid lymphoma, Waldenströms macroglobulinemia, follicular center lymphoma, mucosa-associated lymphoid tissue lymphoma, hairy cell leukemia, diffuse large B-cell lymphoma, Burkitts lymphoma, and node based moncocytoid lymphoma.

84. The method of claim 12, wherein the organism expresses a genetic defect resulting in defective B cell receptor mediated transmembrane signaling in B cells.

85. The method in claim 84, in which the defective B cell receptor mediated transmembrane signaling is caused by altered expression of CD19, CD22 or Lyn.